REMARKS

Claims 18 and 25-35 are pending in the application. Claims 1-17 and 19-24 were previously canceled. Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender (U.S. Patent No. 4,336,185, hereafter "Niswender") in view of Wedeking et al. (U.S. Patent No. 6,093,382; hereafter "Wedeking") and Sinkule et al. (European Patent Application No. 0282057; hereafter "Sinkule"). Claims 18, 25-28, and 30-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Goldenberg (U.S. Patent No. 5,698,178; hereafter "Goldenberg"). Applicants address each of these rejections below.

As an initial matter, Applicants wish to thank Examiner Perreira for the helpful telephonic interview conducted with Dr. Jan Tittel of Clark & Elbing LLP on February 10, 2009. Applicants herein present a response to the issues raised by Examiner Perreira during the interview regarding obviousness of the present claims over the cited art.

The Claimed Invention

Claim 18 is directed to a method of targeting a radionuclide to a malignant cell within a subject, where the malignant cell expresses a tumor associated antigen and expresses folate binding protein. This method involves (i) coupling an antibody, antibody fragment, or antibody construct having affinity for the tumor associated antigen to at least one non-cytotoxic folate to form a dual binding conjugate, (ii) coupling the radionuclide to the dual binding conjugate, and (iii) administering the radionuclide coupled to the dual binding conjugate to the subject.

Claim 31 is directed to a conjugate consisting of (i) a radionuclide, (ii) an antibody, antibody fragment, or antibody construct, with affinity for a tumor associated antigen, and (iii) at least one non-cytotoxic folate.

The remaining claims depend from either claim 18 or 31.

The conjugates recited in the present claims can target a malignant cell using both

the antibody or antibody fragment moiety *and* the non-cytotoxic folate moiety. This concept is neither taught nor suggested in the cited art.

Rejections Under 35 U.S.C. § 103(a)

Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Sinkule. Claims 18, 25-28, and 30-35 are also rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Goldenberg. These bases for the obviousness rejection are addressed, in turn, as follows.

The combination of Niswender, Wedeking, and Sinkule

The Office states (page 3):

> Niswender teaches a receptor binding conjugate that may comprise three components, 1.) folic acid and salts, esters, and amides thereof, 2.) an antibody, such as a gamma globulin…and/or 3.) a radionuclide or radionuclides.

As discussed during the interview, Applicants submit that the chemical formula disclosed in Niswender does not encompass or suggest the claimed conjugates. In the formula disclosed in Niswender (column 1, lines 17-64) "one of R or R^1 is a carboxy, or a salt or amide thereof" (see lines 63-64). Thus, because one of R or R^1 must be a carboxy, or a salt or amide thereof, only one position remains, which can accommodate either a protein radical, such as gamma globulin, or a cyclic radical A, which may then be radiolabeled. This is also evident in the Examples in Niswender, where only folate-thyroglobulin or folate-radiotyrosine are generated, and in the claims which state that "one of the R and R^1 substituents is carboxy or a salt, ester or a mono- or di-alkyl amide thereof and the other R or R^1 substituent is said radical." As such, Niswender does not teach or suggest a conjugate including an antibody (or antibody fragment) *and* a non-cytotoxic folate moiety.

Turning to the other cited references, the Office states (page 4):

> Wedeking et al. was used to teach of a gadolinium-folate (folic acid) conjugate comprising multiple folates (folic acid) conjugated to a radionuclide chelate capable of binding gadolinium. It would be predictable to include an antibody into the conjugates of Wedeking et al. to provide site-specific targeting as Sinkule et al. teaches that an antibody may be used for a wide variety of target antigens.

And states (page 5):

> Sinkule et al. was not used to teach of replacing of the toxic folic acid with a non-toxic folic acid. Sinkule was used to teach that an antibody may be used as a target entity.

Applicants submit that none of the cited references, alone or in combination, teach or suggest a conjugate that includes a non-cytotoxic folate as well as an antibody or antibody fragment with affinity for a tumor associated antigen, much less why it would be advantageous to generate such a conjugate.

Wedeking does not describe or suggest conjugates containing a folate *and* an antibody. The conjugates of Wedeking do not include an antibody or antibody fragment and Wedeking does not in any way suggest including an antibody or antibody fragment in its conjugates.

Sinkule describes conjugates containing a tumor-specific antibody conjugated to a chemotherapeutic agent. In particular, Sinkule states (column 2, lines 24-30):

> A chemo-radio-immuno-conjugate of the present invention comprises a conjugate of a chemotherapeutic agent, a radionuclide, and an antibody. Preferably the chemotherapeutic agent is selected from ... folic acid analogs (anti-fols).

Sinkule further states (column 2, lines 16-20):

> The radioactive component is used to potentiate the therapeutic effect of the chemotherapeutic agent of the conjugate although it can, in some cases, also be used to monitor the distribution of the conjugate in vivo.

And states (column 2, lines 40-45):

> By the term chemotherapeutic agent is meant a low molecular weight, i.e.,

> less than 10,000 MW, chemotherapeutic agent *clinically useful against solid tumors, leukemias, viral infections or a variety of malignancies and pathological states*. (Emphasis added.)

Clearly, in accordance with definition of a chemotherapeutic agent in Sinkule, the folic acid analogs that may be included in the conjugates described in Sinkule must be clinically useful against malignancies and pathological states. As is evident from the cited passages, the radionuclide component of the Sinkule conjugate at best potentiates the therapeutic effect of the chemotherapeutic agent. In contrast, Applicants' claims require the folate to be non-cytotoxic; it is the radionuclide in Applicants' claimed conjugates that provides the therapeutic effect. In short, if anything, Sinkule teaches away from using a non-cytotoxic folate in a conjugate containing an antibody or antibody fragment and a radionuclide. As such, Sinkule provides no suggestion or motivation to a skilled artisan to include the folate of Wedeking in a conjugate containing an antibody (or antibody fragment) and a radionuclide.

Moreover, Applicants submit that the synthesis of conjugates containing an antibody (or antibody fragment), a radionuclide, and a non-cytotoxic folate, while maintaining the targeting ability of both the antibody and folate components, is more difficult than the synthesis of conjugate containing only a radionuclide and either an antibody or a non-cytotoxic folate. Nothing in the cited art, even if combined, suggests the targeting efficacy of the conjugates encompassed by the present claims. In contrast, Applicants, for instance, in Example 5 of the specification, teach that "[a]ntibodies labeled with folate can in principle react with both the antigen and folate binding protein, i.e., such conjugate possesses dual binding ability." Applicants submit that nothing in the cited art would give a skilled artisan a reasonable expectation of success for use of the Applicants' invention prior to the Applicants' disclosure.

For all the above reasons, Applicants submit that the rejection of claims 18 and 25-35 under 35 U.S.C. § 103 over the combination of Niswender, Wedeking, and Sinkule

should be withdrawn.

The combination of Niswender, Wedeking, and Goldenberg

The Office states (pages 7 and 8):

> Goldenberg was used to teach of receptor binding conjugates comprising various targeting antibodies and at least one diagnostic or therapeutic agent ... It would have been predictable for one skilled in the art to substitute the antibodies of Goldenberg for the antibodies of the conjugates of the combined disclosures of Niswender and Wedeking to provide for targeting of the conjugates.

The disclosures of Niswender and Wedeking are discussed above. For the reasons provided above, Applicants submit that Niswender and Wedeking, alone or in combination, do not describe or suggest a conjugate including a non-cytotoxic folate *and* an antibody or antibody fragment. Goldenberg does not cure this deficiency.

Goldenberg discloses immunoconjugates that contain an antibody that binds to a multidrug transporter protein, an antibody that binds to a tumor-associated antigen or infectious agent antigen, and a therapeutic or diagnostic agent. Goldenberg states (column 23, lines 45-48):

> [T]herapeutically useful polyspecific immunoconjugates can be prepared in which an antibody composite is conjugated to a toxin or a chemotherapeutic drug.

And states (column 23, lines 55-58):

> Useful cancer chemotherapeutic drugs for the preparation of polyspecific immunoconjugates include ... folic acid analogs.

Clearly the folic acid analogs described in Goldenberg must function as a chemotherapeutic and, therefore, are cytotoxic. A non-cytotoxic folate as recited in the present claims would not have this function. Hence, Applicants submit that one skilled in the art, in view of Goldenberg, would not be motivated to combine an antibody (or

antibody fragment) with a radionuclide *and* a *non-cytotoxic folate* as required by the present claims. There simply is no reason provided in the combination of Goldenberg with Niswender and Wedeking for one skilled in the art to generate the conjugates recited in Applicants' claims, much less an expectation of success in maintaining the binding (and therefore targeting) affinities of both the antibody and non-cytotoxic folate components of the conjugate.

Applicants respectfully request that this basis for rejection also be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested. However, should there be any remaining issues, Applicants respectfully request that the Examiner contact the undersigned by telephone prior to issuing an Office Action.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including February 13, 2009, and an authorization to charge the required extension fee to Deposit Account No. 03-2095.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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